IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Application of: Moshe Baru et al.

Serial No.: 10/553,357 Art Unit: 1654

Date Filed: July 13, 2006 Examiner: Ha, Julie

For: PHARMACEUTICAL COMPOSITION COMPRISING PROTEINS AND/OR POLYPEPTIDES AND COLLOIDAL PARTICLES

DECLARATION UNDER 37 CFR §1.132

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Sir:

I, Moshe Baru, an Israeli citizen residing at Hahadarim Pinat Tarpat St., Pardes Hana, Israel, hereby declare and state as follows:

1. I am the General Manager and Chief Scientist, Omri Laboratories Ltd, Nes-Ziona, Israel, a wholly-owned subsidiary of Opperbas Holding B.V., the assignee of record in the above-identified application, and my educational and professional experience was presented in Annex A of the declaration under 37 CFR §1.132 filed with the response of January 4, 2008.
2. I am a co-inventor and am familiar with the contents of U.S. Application No. 10/553,357 (hereinafter: *the application*). The application describes a pharmaceutical composition for parenteral administration comprising a therapeutically

effective amount of a protein or polypeptide and colloidal particles as defined in the claims (hereinafter: *the invention*).

3. In the present Declaration, I wish to provide further evidence that the description of the invention in the application enables a scientist skilled in the field of the invention to apply the invention to other proteins and polypeptides. In the attached Annex A, I describe experimental results using a composition comprising copaxone prepared according to the invention for the treatment of acute colitis, using the dextran sodium sulfate (DSS) model. This indication differs significantly from the treatment of hemophilia which is described in the application.

4. It may be seen from the results of the experiment that the composition of the invention may be used to enhance the therapeutic effect of the proteins and polypeptides defined in the claims of the application.

5. Furthermore, the above results provide a reasonable basis for the assumption that a composition comprising copaxone prepared according to the invention may be used to treat other diseases for which copaxone is known to be effective, including multiple sclerosis (MS), including the experimental autoimmune encephalomyelitis (EAE) model for MS, experimental hepatic fibrosis model (Horani A, Muhanna N, Pappo O, Melhem A,

Alvarez CE, Doron S, Wehbi W, Dimitrios K, Friedman SL, Safadi R. Beneficial effect of glatiramer acetate (Copaxone) on immune modulation of experimental hepatic fibrosis. *Am J Physiol Gastrointest Liver Physiol* 2007; 292: G628-G638), hSOD1-G93A mouse model of amyotrophic lateral sclerosis (ALS) (Habisch HJ, Schwalenstöcker B, Danzeisen R, Neuhaus O, Hartung HP, Ludolph A. Limited effects of glatiramer acetate in the high-copy number hSOD1-G93A mouse model of ALS. *Exp Neurol*. 2007; 206(2):288-95), dextran sodium sulfate (DSS) and trinitrobenzene sulfonic acid (TNBS) models for inflammatory bowel disease (IBD) (Aharoni R, Kayhan B, Arnon R. Therapeutic effect of the immunomodulator glatiramer acetate on trinitrobenzene sulfonic acid-induced experimental colitis. *Inflamm Bowel Dis* 2005; 11: 106-15; Aharoni R, Kayhan B, Brenner O, Domev H, Labunskay G, Arnon R. Immunomodulatory therapeutic effect of glatiramer acetate on several murine models of inflammatory bowel disease. *J Pharmacol Exp Ther* 2006; 318: 68-78; Gur C, Karussis D, Golden E, Doron S, Ilan Y, Safadi R. Amelioration of experimental colitis by Copaxone is associated with class-II-restricted CD4 immune blocking. *Clin Immunol* 2006; 118: 307-16). Since Copaxone is effective in those diseases, it can be concluded that, as was demonstrated in acute colitis, formulation with PEGLip will

improves the efficacy of Copaxone in other inflammation and autoimmune diseases.

6. The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

May 29, 2008
Date

Moshe Baru
Dr. Moshe Baru

ANNEX A

Enhancement of the therapoetic efficacy of Copaxone in acute colitis model by formulation with PEGylated liposomes

Introduction

Inflammatory bowel diseases (IBD), mainly ulcerative colitis (UC) and Crohn's disease (CD) are complex multifactor immunological disorders which characterized by gut inflammation and mucosal damage. The dextran sodium sulfate (DSS) model, firstly reported by Ohkusa (Ohkusa T. Production of experimental ulcerative colitis in hamsters by dextran sulfate sodium and change in intestinal microflora. *Jpn J Gastroenterol* 1985; 82: 1327-36) as a hamster model and later adapted to mice by Okayasu and colleagues (Okayasu I, Hatakeyama S, Yamada M, Ohkusa T, Inagaki Y, Nakaya R. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. *Gastroenterology* 1990; 98: 694-702), belongs to the chemically induced models of IBD. In general, acute colitis is induced in mice by administering DSS in the drinking water in a concentration ranging from 1%-5% for several days followed by untreated water. The clinical features of this model include weight loss, loose stools/ diarrhea, rectal bleeding, and shortening of the colon. These phenotypic features are of relevance to human UC.

Material and methods

C57Bl mice (8-10 weeks, 18-20 g) were randomized into 5 groups each including 9 animals. Acute colitis was induced by administration of DSS (MP Biomedicals, France, 2% wt./v) in the drinking water for 5 days followed by untreated water for additional 5 days. From initiation of the study, mice of three groups were injected daily subcutaneously with 200µl/ mice of Copaxone (Teva, Israel, 100 mg/kg), PEGylated liposomes (PEGLip) (4.5% weight lipids/volume), or PEGLip-Copaxone (4.5% weight lipids/volume, 100 mg Copaxone/kg). Groups of untreated mice and DSS-treated mice were used as normal and reference groups. Mice weight, overall diarrhea, rectal bleeding and survival were monitored daily. Ten days following initiation of the study, all mice were sacrificed and the intestine length was recorded.

Results

All mice survived the study.

Measurements of column length at the end of the study indicated that a treatment by PEGLip-Copaxone was the most effective in protecting the colon. The average and median colon length of this group was 7.5 and 7.7 cm, respectively (Table I, Fig. 1). Colon length of this group was not statistically different from that of control untreated mice (Table I). In contrast, the average and median colon length of standard Copaxone treated mice were 7.2 and 7.4 cm, respectively (Table I, Fig. 1). Colon length of this group was statistically different ($p=0.049$) from that of control untreated mice (Table I). The proportion of healthy or mildly affected mice (colon length >7.6) showed similarity between PEGLip-Copaxone treated mice and normal mice (81 and 89% healthy/mildly affected mice). However, groups treated by standard Copaxone or PEGLip only were found to be similar to the negative control DSS group mice (22-33% healthy/mildly affected mice, Fig. 2).

The weight gain of mice, treated with PEGLip-Copaxone, was similar to that of normal mice and statistically different from negative control DSS treated group (Fig. 3). Other groups including that of standard Copaxone treated mice were not statistically different from negative control DSS treated mice (Fig. 3).

The data described above indicate that formulation with PEGLip increased the efficacy of Copaxone.

Table I: Colon length (cm) of mice following DSS administration and various treatments

			DSS +		
	Normal mice	DSS	Copaxone	PEGLip	PEGLip-copaxone
Average ± SD (cm)	8.0 ± 0.4	7.2 ± 0.9	7.2 ± 1.1	7.1 ±0.7	7.5 ± 0.8
Median (cm)	8.2	6.9	7.4	7.2	7.7
t-test *vs.* 'normal'		0.016	0.049	0.003	0.102

Fig 1. Median colon length

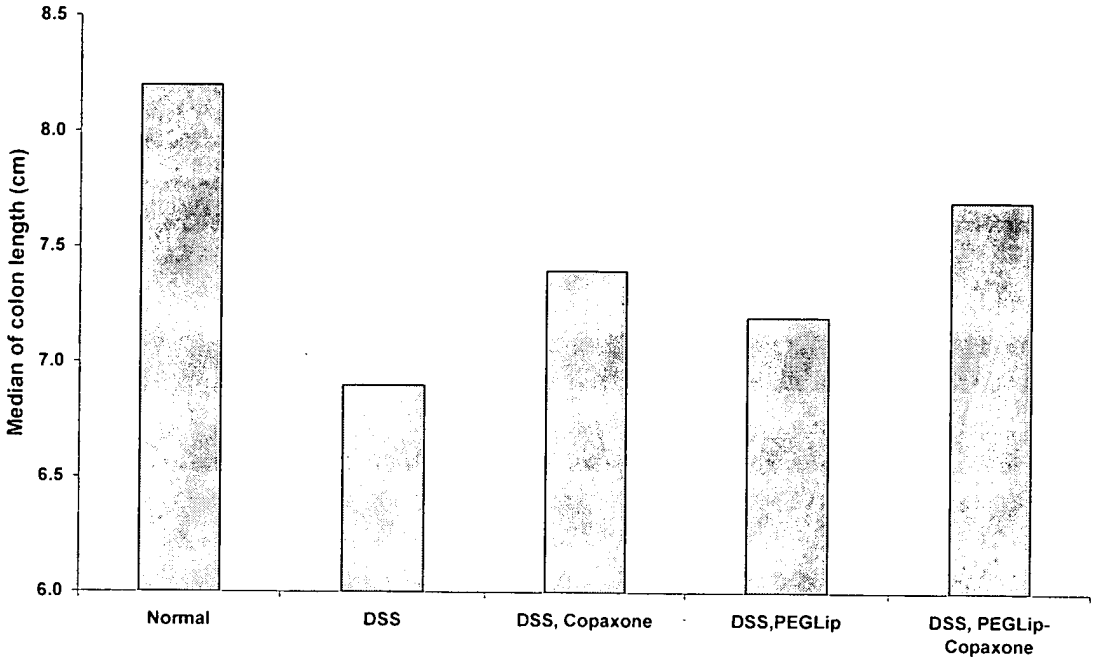


Fig 2. Healthy/mild affected Mice (colon length ≥ 7.6 cm)

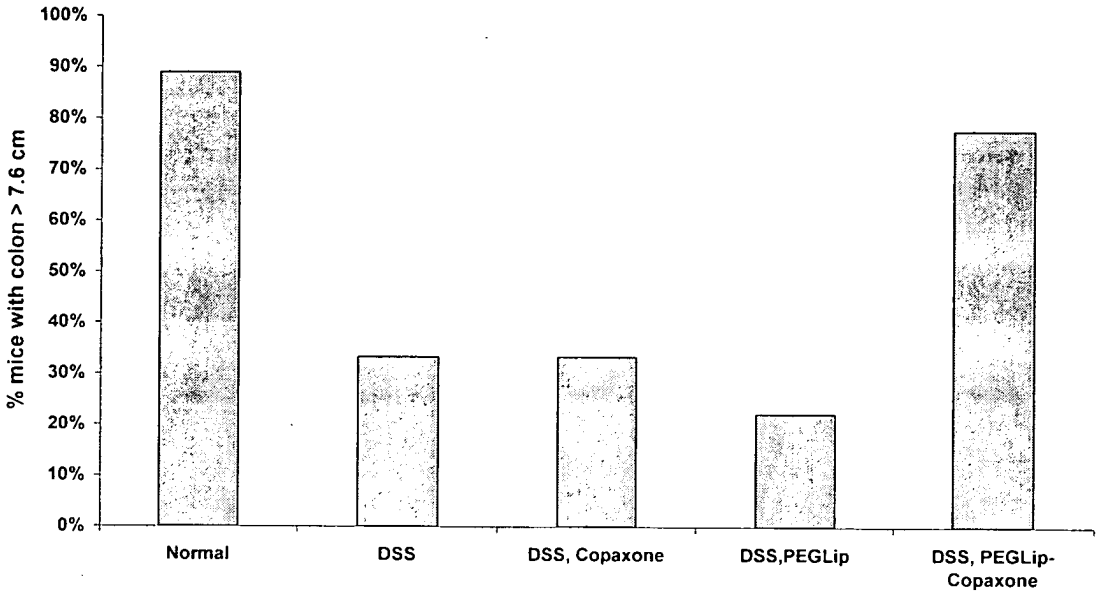
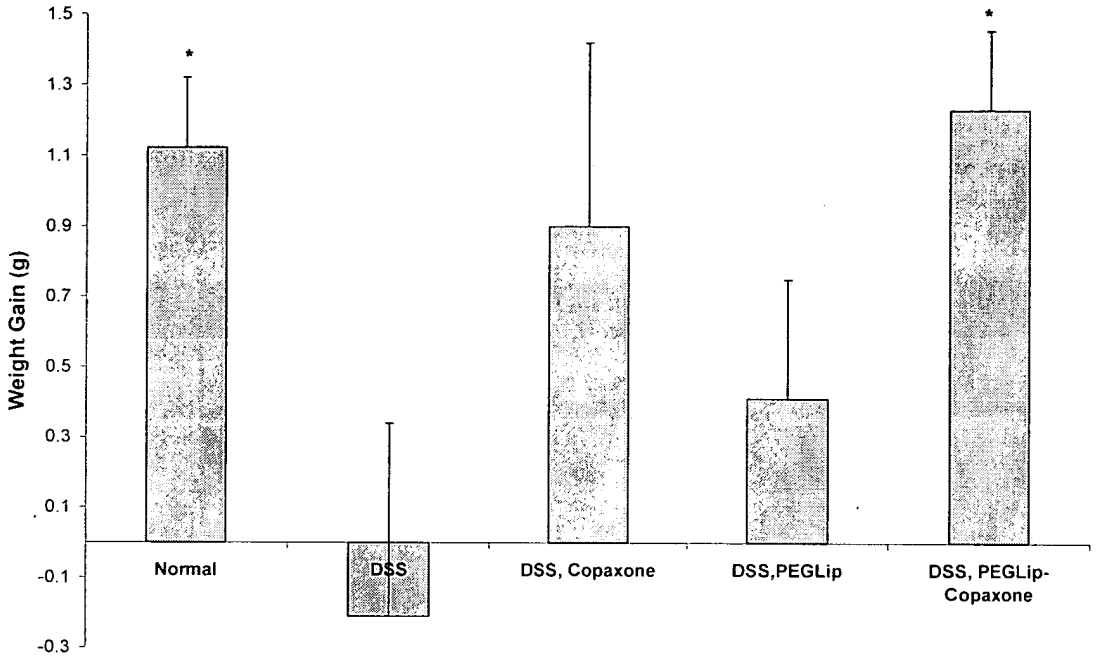


Fig 3. Average weight gain (mean ± SEM)



* - Statistical significant ($p< 0.05$, t-test) versus DSS treated mice

Conclusion

The results indicate that formulation with PEGLip improves the efficacy of copaxone in the treatment of acute colitis. This was found in the 3 main parameters characterizing the disease: 1. Colon length. 2. Degree of disease (% of mice with a colon length of > 7.6 cm). 3. Weight gain.